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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/448,649	05/24/95	MASINOVSKY B	27866/32663

HM11/0914

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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/14/98

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 34

Serial Number: 08/448649
Filing Date: 5/24/95
Appellant(s): Masinovsky et al.

Mailed
Sept. 14, 1998
Group 1600

Li-Hsien Rin-Laures
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on Appeal filed 7/10/98 (Paper No. 34).

The text of those sections of Title 35 U.S.Code not included in this Appeal can be found in a previous Office action herein.

(1) **Real Party of Interest.**

A statement identifying the real party of interest ~~is~~ is contained in the Brief.

(2) **Related Appeals and Interferences Identified.**

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) **Status of Claims.**

The statement of the status of claims contained in the Brief is incorrect.

This Appeal involves claims 30-33.

(4) **Status of Amendments After Final.**

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Invention.

The Summary of Invention contained in the Brief is correct.

A key element and intent encompassed by the claimed methods on page 4, last two sentences of paragraph 1 of the Summary of the Invention in the Brief is set forth as follows. "Blocking adhesion of hemopoietic cells to stromal cells results in release of hemopoietic cells into peripheral blood circulation and provides important therapeutic effects in, for example, the field of bone marrow transplantation. In bone marrow donors, release of hemopoietic precursor cells allows these cells to be easily harvested from the peripheral blood, while in bone marrow recipients, release of hemopoietic cells could be used as part of a regime to eliminate the recipients's own bone marrow prior to transplantation."

Appellant's arguments and declaratory evidence and the rejections of record set forth herein focus on this key element of the claimed invention. In contrast to appellant's assertions and reliance on declaratory evidence, the rejections of record indicate that there is insufficient written support in the specification as filed for this key element of the claimed invention, drawn to methods of blocking the interaction between a bone marrow stromal cell expressing VCAM-1 and a cell expressing VLA-4 encompassing hemopoietic stem and progenitor cells for the purpose of harvesting or peripheralizing hemopoietic cells for bone marrow transplantation.

(6) Issues.

The appellant's statement of the issues in the Brief is incorrect.

Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide written support for the invention as now claimed: "a method of blocking interaction between bone marrow stromal cells expressing VCAM-1 and a cell expressing VLA-4 (wherein the cell expressing VLA-4 is a hemopoietic precursor cell) (wherein the cell expressing VLA-4 is a hemopoietic precursor cell expressing CD34 antigen) which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and the cell expressing VLA-4"

The specification is objected to and claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, as to "how to use" VCAM-1-specific antibodies in "a method of blocking interaction between a bone marrow stromal cells expressing VCAM-1 and a cell (hemopoietic precursor cell, hemopoietic stem or progenitor cells) expressing VLA-4 which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and a cell expressing VLA-4", particularly as this encompasses peripheralizing/mobilizing and harvesting hemopoietic cells for bone marrow transplantation.

Also, see the Summary of the Invention section above for the key element and intent encompassed by the claimed methods and the issues addressed herein with respect to peripheralizing/mobilizing and harvesting hemopoietic stem and progenitor cells for bone marrow transplantation.

(7) Grouping of Claims.

The appellant's statement in the Brief that certain claims do not stand or fall together is not agreed with because the scope and intent of the claimed methods are drawn to "a method of blocking interaction between bone marrow stromal cells expressing VCAM-1 and a cell expressing VLA-4 " encompassing "hemopoietic stem and progenitor cells" to peripheralize/mobilize or to harvest said hemopoietic cells for the purposes of bone marrow transplantation, as argued by appellant and relied upon by the declarations of record.

Although independent claim 30 recites "a cell expressing VLA-4" which encompasses a variety of cell types including lymphocytes and hemopoietic cells and the dependent claims recite hemopoietic cells which encompasses hemopoietic stem and progenitor cells; the instant claims do not recite "lymphocytes" nor are the claims limited to lymphocytes. In addition, appellant's arguments and declaratory evidence are drawn to peripheralizing/mobilizing and to harvesting hemopoietic cells for bone marrow transplantation and not to inhibiting lymphocyte adherence.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "a method of blocking interaction between bone marrow stromal cells expressing VCAM-1 and a cell expressing VLA-4 (wherein the cell expressing VLA-4 is a hemopoietic precursor cell) (wherein the cell expressing VLA-4 is a hemopoietic precursor cell expressing CD34 antigen) which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and the cell expressing VLA-4".

Appellant 's amendment, filed 9/19/97 (Paper No. 28) similarly to appellant's amendment, filed 12/12/96 (Paper No. 23), has directed support for the amended claims to the following sections of the specification as filed.

(1) page 4, lines 11-16; however said passage refers to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors;

Appellant has relied upon the expression of VLA-4 on lymphocytes throughout the specification. The instant specification discloses inhibiting lymphocyte adherence and migration, however the claims are not drawn to lymphocytes but rather drawn to cells other than lymphocytes. The claims are drawn to "VLA-4 expressing cells" encompassing "a hemopoietic cell expressing CD34 antigen" and "a hemopoietic stem cells or a hemopoietic progenitor cell". It has been noted that page 14, lines 28-32 of the specification similarly refers to blocking lymphocyte adhesion and not hemopoietic precursors.

(2) page 5, lines 14-15 which refers to Figure 12 as described in Example 5 and page 17, lines 24-30 which states: "VLA-4 ... is expressed at high levels on bone marrow cells bearing the CD34" and "that CD34 expression distinguishes a subset of bone marrow cells (1-4% which are enriched in primitive stem cells and progenitors"

Appellant has relied upon the instant disclosure including Example 5 and the expression of VLA-4 on hemopoietic cells, however the specification as filed does not provide written support for blocking hemopoietic cell-stromal cell interactions. The specification provides guidance and direction to use VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as to block lymphocyte binding or to impede lymphocyte or tumor cell transmigration (see Summary of the Invention of the specification, particularly page 4, lines 17-22). With respect to hemopoietic cells, which is the subject of the claimed methods; the specification provides written support as well as guidance and direction to use VCAM-1-specific antibodies to immunoselect hemopoietic stem and progenitor cells and bone marrow stromal elements (page 18, lines 13-15).

Therefore, the rejection of record maintained that there does not appear to be written support for blocking hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there written support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion to inhibit GVHD for example and not towards inhibiting hemopoietic stem and progenitor cell adhesion to bone marrow stromal cells to peripheralize/mobilize said hemopoietic cells, as encompassed and asserted by appellant..

Appellant's arguments in conjunction with the Torok-Storb declaration under 37 C.F.R. § 1.132 have been fully considered but not found convincing and are addressed below in the Response to Argument..

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Adding information to the specification not supported by the disclosure as filed is considered new matter in that introduces new concepts violate the description requirement of the first paragraph of 35 U.S.C. 112.

Enablement

The specification is objected to and claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Appellant's arguments in conjunction with the Torok-Storb and Papayannoupoulo declarations of record are addressed below in the Response to Argument.

As indicated above in the new matter written description rejection, there is insufficient information or guidance as how to use VCAM-1-specific antibodies in "a method of blocking interaction between a bone marrow stromal cells expressing VCAM-1 and a cell (hemopoietic precursor cell, hemopoietic stem or progenitor cells) expressing VLA-4 which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and a cell expressing VLA-4".

The application must be enabled at the time the invention was made.

The specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as to block lymphocyte binding or to impede lymphocyte binding or tumor cell transmigration (see Summary of the Invention in the specification, particularly page 4, lines 17-22). With respect to hemopoietic cells, which is the subject of the claimed methods; the specification provides written support as well as guidance and direction to use VCAM-1-specific antibodies to immunoselect hemopoietic stem and progenitor cells and bone marrow stromal elements (page 18, lines 13-15).

The application as filed does not provide guidance and direction on "how to use" anti-VCAM-1 to block any VCAM-1-mediated adhesion, regardless of the type of cells involved, and, in particular, to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells in order to peripheralize and to harvest hemopoietic cells for bone marrow transplantation.

Therefore, the specification as filed does not provide any guidance on "how to use" the VCAM-1 specific antibodies in the manner encompassed or intended by the claimed methods, as argued by appellant in conjunction with the Torok-Storb and Papayannoupoulo declarations of record (see below for details). The specification is drawn to inhibiting lymphocyte adherence not to inhibiting hemopoietic stem and progenitor cell adherence. The disclosure does not provide sufficient direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods.

The specification does not teach how to extrapolate data obtained from in vitro binding studies of marrow stromal elements to the development of effective in vivo therapeutic methods to block hemopoietic cell-marrow stroma interactions, commensurate in scope with the claimed invention. Undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting hemopoietic cell-marrow stroma interactions in a therapeutic method to peripheralize/mobilize or to harvest hemopoietic stem and progenitor cells.

(10) Response to Argument

Rejection Under 35 U.S.C. § 112, First Paragraph

Written Description

Appellant's arguments in conjunction with the Torok-Storb declaration under 37 C.F.R. § 1.132 (Exhibits D), have been fully considered but are not found convincing.

Upon review of appellant's amendment, filed (Paper No. 26) and appellant's arguments, filed in the Brief; the Papayannoupoulo declaration (Exhibit F) is considered only in light of the enablement rejection and not written description.

Appellant argues that the written description rejection improperly introduced enablement considerations and that the declarations addressing enablement issues were considered in view of enablement. Appellant argues that the insufficiencies of the declaratory evidence or providing any rebuttal evidence to the factual representations of the declarations has not been provided by the rejections of record. Appellant argues that the rejections of record has essentially required an ipsis verbis disclosure, by indicating that the "blocking interaction with an antibody" did not appear in the same sentence. It is noted that the disclosure need only convey with reasonable clarity to persons skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.

Appellant relies upon the Torok-Storb declaration (Exhibit D) that "one of ordinary skill in the art would understand from the application that anti-VCAM-1 antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved, which contradicts the rejection of record which indicates that the instant disclosure only contemplates the use of anti-VCAM-1 antibodies to block adhesion of only one type of cell expressing VLA-4 (i.e. lymphocytes) and not hemopoietic cells. Further appellant provides two Figures to illustrate the role of VLA-4:VCAM-1 interactions between lymphocytes and endothelial cells and hemopoietic precursors and bone marrow stromal cells. Appellant then relies upon the Torok-Storb statement that "there is no indication in the application that the use of VCAM-1 specific antibodies to interfere with or block intercellular adhesive interactions is limited to only some of the disclosed VCAM-1-mediated interactions and not others". Therefore, appellant asserts that this declaration demonstrates that the specification conveys with reasonable clarity that anti-VCAM-1 antibodies are useful for the broad genus of methods for blocking adhesion between any cell expressing VCAM-1 and any cell expressing VLA-4. Appellant then argues that given the specification's identification of VCAM-1 on bone marrow stromal cells; the subgenus of such VCAM-1/VLA-4 interactions between bone marrow stromal cells expressing VCAM-1 and cells expressing VLA-4, including the interaction between said stromal cells and hemopoietic precursor cells, is clearly recognizable.

In addition, appellant relies upon In re Alton 37 USPQ2d, 1578 (Fed. Cir. 1996) to support the Torok-Storb declaratory evidence of record. Appellant asserts that the rejection of record summarily concluded that the rejection should be maintained and did not provide an explanation of why the declaratory evidence was not sufficient. Appellant acknowledges that the rejection of record pointed out the Torok-Storb declaration indicated that "one of ordinary skill in the art would understand from reading the application that anti-VCAM antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved and that one of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4/VCAM-1 interaction to another. Appellant asserts that this declaration nowhere states that the conclusions are drawn from what was obvious to one of ordinary skill in the art at the time, but rather what one of ordinary skill in the art would understand from reading the application.

Appellant argues that the consideration of "guidance and direction" and "how to use" would be proper for enablement issues, such issues are not properly addressed in the written description context. Appellant argues that if these are the bases for disregarding the declaratory evidence presented on the issued of written description this basis was in error.

In contrast to appellant's assertions that the insufficiencies of the declaratory evidence or providing any rebuttal evidence to the factual representations of the declarations, the rejection of record has taken into account these declarations, but has been maintained in view of the specification as filed. The new matter rejection of record has relied upon the lack of written description for the claimed invention, as asserted by appellant and the Torok-Storb declaration. The new matter rejection has pointed out how the claimed methods do not find written support in the specification as filed. In addition to the lack of clear written support per se and acknowledged by appellant, the rejection of record further pointed out issues that are lacking in view of appellant's arguments and declaratory evidence of what is intended and encompassed by the instant methods.

Also, it is noted that precisely how close the original description must come to comply with the written description requirement of section 112 must be determined on a case-by-case basis. See In re Alton 37 USPQ2d 1578, 1581 (Fed. Cir. 1996) citing Eiselstein v. Frank, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) and Vas-Cath 19 USPQ2d , 1111, 1116 (Fed. Cir. 1991).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention and that the invention, in that context, is whatever is now claimed.. See MPEP 2163.02. Also, the failure to meet the written description requirement under 35 USC 112, first paragraph arises when the claims are changed after the filing date to change the scope of the disclosure, which does encompass setting forth subgeneric claims (see MPEP 2163.05).

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Here, the instant application has been held deficient under 35 USC 112, first paragraph, because the written description in the specification as filed is not adequate to identify what the appellant now claims or has invented.

The purpose of the written description requirement is broader that to merely explain "how to make and use". However, the context of the written description in the application as filed including issues of "how to use" have been relied upon by the rejections of record, in part, to provide an explanation why the specification as filed lacks adequate written support for the claimed methods.

As pointed out above in the Summary of the Invention section in the Examiner's Answer; a key element and intent encompassed by the claimed methods on page 4, last two sentences of paragraph 1 of the Summary of the Invention in the Brief is set forth as follows. "Blocking adhesion of hemopoietic cells to stromal cells results in release of hemopoietic cells into peripheral blood circulation and provides important therapeutic effects in, for example, the field of bone marrow transplantation. In bone marrow donors, release of hemopoietic precursor cells allows these cells to be easily harvested from the peripheral blood, while in bone marrow recipients, release of hemopoietic cells could be used as part of a regime to eliminate the recipients's own bone marrow prior to transplantation."

Appellant's arguments and declaratory evidence and the rejections of record set forth herein focus on this key element of the claimed invention. In contrast to appellant's assertions and reliance on declaratory evidence, the rejections of record indicate that there is insufficient written support for this key element of the claimed invention, drawn to methods of blocking the interaction between a bone marrow stromal cell expressing VCAM-1 and a cell expressing VLA-4 encompassing hemopoietic stem and progenitor cells for the purpose of peripheralizing/mobilizing or harvesting hemopoietic stem and progenitor cells for bone marrow transplantation in the specification as filed.

As pointed out of record, it is the clear intention of appellant's claimed methods in conjunction with appellant's arguments and declaratory evidence that the claimed methods are drawn to block hemopoietic cell - stromal cell interactions with VCAM-1-specific antibodies in order to peripheralize/mobilize and to harvest hemopoietic stem and progenitor cells.

Although appellant argues that the claims encompass VLA-4 expressing cells, which includes lymphocytes, lymphocytes are not claimed nor are they the subject or focus of the appellant's arguments and declaratory evidence.

Both appellant (see section 8A on pages 6-7 of the Brief) and the rejections of record have focused on the following sections of the instant specification as filed for the written description of the claimed invention, particularly as it applies to blocking adhesion between VLA-4 expressing cells (e.g. hemopoietic stem and progenitor cells) and the bone marrow stromal cells, particularly as it applies to the peripheralizing/mobilizing or harvesting of hemopoietic cells for bone marrow transplantation, which has been the subject of both appellant's arguments and the rejection of record.

Appellant has relied upon the Background of the Invention on page 2, lines 33-36 of the instant specification, which notes the role of VCAM-1/VLA-4 interactions between endothelial cells expressing VCAM-1 and lymphocytes expressing VLA-4. However, the instant claims are drawn to methods of blocking interaction between a bone marrow stromal cells expressing VCAM-1 (versus endothelial cells) and a cell expressing VLA-4 (encompassing hemopoietic stem and progenitor cells versus lymphocytes).

Appellant has relied upon page 17, lines 3-14 and 24-33 of the instant specification to support the role of VCAM-1/VLA-4 interactions in adhesion between bone marrow stromal cells expressing VCAM-1 and hemopoietic cells expressing VLA-4 (disclosed role of interactions versus claimed blocking said interactions by administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1 mediated adhesion between the bone marrow stromal cells and the cell expressing VLA-4, including the peripheralization and harvesting of hemopoietic stem and progenitor cells for bone marrow transplantation).

Appellant has relied upon the Summary of the Invention on page 4, lines 11-16 of the instant specification to support the ability to block binding of lymphocytes which express VLA-4 to endothelial cells which express VCAM-1 (disclosed lymphocyte-endothelial interactions versus claimed blocking VLA-4 expressing cells to bone marrow stromal cells) and most preferably by the ability to bind human VCAM-1 and bone marrow stromal cells expressing VCAM-1 (disclosed binding of agent to bone marrow stroma versus claimed blocking interaction between VLA-4 expressing cells to bone marrow stroma).

Page 18, paragraphs 1-5 of the instant specification provides further guidance as to the nature of the disclosed methods of the instant application as filed. Here, the following methods employing VCAM-1-specific antibodies are disclosed. VCAM-1-specific antibodies are useful for preventing graft-versus-host disease in bone marrow transplantation (paragraph 1) (disclosed anti-inflammatory/lymphocyte methods versus claimed and asserted peripheralization/mobilization of hemopoietic stem or progenitor cells). VCAM-1 specific antibodies can be used to immunoselect bone marrow stromal elements (paragraph 2) (disclosed immunoselection versus claimed and asserted inhibiting adhesion of hemopoietic cells to bone marrow stroma). VCAM-1 antibodies can be conjugated to radionuclides or other pharmaceutical moieties to provide targeting devices to achieve high specific localization of said agents to the bone marrow for radioimaging or therapy or neoplastic disease, anemia or benign hyperplasias of hemopoietic origin (paragraph 4) or said antibody conjugates in combination with IL-4/TNF-α to achieve enhanced specificity of the antibody conjugate to the bone marrow (paragraph 5) (disclosed targeting versus claimed and asserted inhibiting).

Therefore in the context of bone marrow transplantation; the instant specification as filed discloses:
VCAM-1-specific antibodies are employed in methods to inhibit an immune response with respect to lymphocyte responses (versus blocking adhesion of VLA-4 expressing cells to promote the peripheralization of hemopoietic stem and progenitor cells);
VCAM-1-specific antibodies are employed in methods to immunoselect (versus blocking adhesion to promote the peripheralization of hemopoietic stem and progenitor cells); and
VCAM-1-specific antibodies are conjugated to target pharmaceutical moieties of interest.

Neither appellant's Summary of the Invention nor the Torok-Storb declaration direct written support to the specification as filed for blocking adhesion between VLA-4 expressing cells (e.g. hemopoietic stem and progenitor cells) and the bone marrow stromal cells, nor direct written support to the specification as filed for methods to peripheralize/mobilize or to harvest hemopoietic cells for bone marrow transplantation, nor direct written support to the specification as filed for the claimed methods to encompass said methods to peripheralize/mobilize and to harvest hemopoietic cells, which has been the subject of both appellant's arguments and the rejection of record.

In contrast to written support as well as guidance and direction in the specification as filed, appellant's arguments in conjunction with the declaratory evidence have inferred the claimed methods including that the intent of the claimed methods to encompass to peripheralize/mobilize and to harvest hemopoietic cells

While the instant specification provides written support to inhibit graft-versus-host-disease with anti-VCAM antibodies due to their effects on lymphocytes and provides written support for the use of IL-4 and TNF-α cytokines to enhance the growth of the bone marrow graft; there is no written support for blocking adhesion between VLA-4 expressing cells (e.g. hemopoietic stem and progenitor cells) and the bone marrow stromal cells, particularly as it applies to the peripheralization or harvesting of hemopoietic cells for bone marrow transplantation, which has been the subject of both appellant's arguments and the rejection of record.

Appellant relies upon the Torok-Storb statement that "there is no indication in the application that the use of VCAM-1 specific antibodies to interfere with or block intercellular adhesive interactions is limited to only some of the disclosed VCAM-1-mediated interactions and not others" to demonstrate that the specification conveys with reasonable clarity that anti-VCAM-1 antibodies are useful for the broad genus of methods for blocking adhesion between any cell expressing VCAM-1 and any cell expressing VLA-4. Appellant relies upon the specification's identification of VCAM-1 on bone marrow stromal cells to support the subgenus of blocking adhesion between VLA-4 expressing cells (e.g. hemopoietic stem and progenitor cells) and the bone marrow stromal cells, particularly as it applies to the peripheralization/ mobilization or harvesting of hemopoietic cells for bone marrow transplantation

Given the lack of written description in the specification as filed of the claimed methods per se as well as an absence of a written description of peripheralizing or harvesting hemopoietic stem and progenitor cells by blocking VLA-4-expressing cell:VCAM stromal cell interactions; appellant's arguments and declaratory evidence are not found persuasive as it relates to setting forth this new subgenus now claimed and asserted by appellant.

Further it is noted that while appellant argues that obviousness is not being relied upon; appellant is relying upon generic blocking of anti-VCAM antibodies of VCAM-1-mediated adhesion and the binding of hemopoietic cells to stromal cells to claim a new previously undisclosed use of anti-VCAM antibodies. Obviousness is not the standard for the addition new limitations to the disclosure as filed.

It is clear from the written support and the context of the specification as filed, appellant was not in possession of blocking adhesion between VLA-4 expressing cells (e.g. hemopoietic stem and progenitor cells) and the bone marrow stromal cells, particularly as it applies to the peripheralization/mobilization or harvesting of hemopoietic cells for bone marrow transplantation

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Adding information to the specification not supported by the disclosure as filed is considered new matter in that introduces new concepts violate the description requirement of the first paragraph of 35 U.S.C. 112.

Appellant's arguments are not found persuasive.

Enablement

Appellant's arguments in conjunction with the Torok-Storb and the Papayannoupoulo declarations under 37 C.F.R. § 1.132, filed 8/22/96 (Paper No. 26), have been fully considered but are not found convincing.

Appellant argues that the enablement rejection improperly introduced written description considerations and that the declarations addressing enablement issues were considered in view of written description. Appellant argues that the rejection based on lack of guidance and direction is merely because there is not an ipsis verbis recitation of the claimed method. Appellant argues that consideration of information known in the art and whether one of ordinary skill in the art could have used anti-VCAM-1 antibodies according to the claimed methods without undue experimentation and asserts that there has not been a consideration of these questions in the rejections of record.

Appellant relies upon In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) and known therapeutic application of antibodies in general to block the interaction between two molecules by administering an antibody that binds to one of these molecules. Appellant argues that the instant specification provides guidance and direction between bone marrow stromal cells and hemopoietic cells and examples of blocking the adhesion of lymphocytes to endothelial cells and that the anti-VCAM antibody 6G10 binds bone marrow stromal cells to support the instant methods. Appellant argues that the Torok-Storb and the Papayannoupoulo declarations show that quantity of experimentation required to block adhesion of these stromal cells to hemopoietic cells which express VLA-4 was negligible.

Appellant asserts that there has been a failure to point out any difficulties the ordinary artisan would have had in carrying out the claimed methods. Here, appellant states that it is a simple matter for one to administer an anti-VCAM-1 antibody, by intravenous injection and to measure the resulting release of hemopoietic cells into the peripheral blood, by taking blood samples and determining the number of hemopoietic colony forming units in each sample

Appellant relies upon the Papayannoupoulo declaration to indicate that the claimed methods were carried out without undue experimentation. Systemic administration of anti-VCAM-1 antibodies in mice caused release of bone marrow progenitor cells from the bone marrow to the peripheral blood, as measure by counting hemopoietic colony forming units in peripheral blood. Appellant relies upon the Papayannoupoulo declaration to indicate that it would have required no more than routine experimentation for the ordinary artisan to determine what therapeutic conditions would provide a desired level of measured response, with respect to the determine the level of decrease in adhesion needed to achieve any desired effect.

Appellant relies upon the Torok-Storb declaration to indicate that after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells, would have understood from the disclosure in the application that a clear therapeutic benefit of administering anti-VCAM-1 antibody to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of hemopoietic progenitor/stromal cell binding and the consequential release of bone marrow cells into the bloodstream would allow these cells to be harvested directly from the blood of a donor. In addition, the advantages of harvesting said cells are discussed.

However, neither the Papayannoupoulo declaration or Torok-Storb declaration provide sufficient direction or guidance in the specification as filed to cause or to measure the resulting release of hemopoietic cells into the peripheral blood or to interrupt hemopoietic progenitor/stromal cell binding in order to release of bone marrow cells into the bloodstream in order for these cells to be harvested directly from the blood of a donor.

Appellant argues that the rejection of record did not identify any errors or deficiencies in the declarations of record nor any difficulties that one of ordinary art would encounter upon carrying out the claimed methods.

In contrast to appellant's assertions that the insufficiencies of the declaratory evidence or providing any rebuttal evidence to the factual representations of the declarations, the rejection of record has taken into account these declarations, but has been maintained in view of the specification as filed.

In contrast to appellant's reliance on the Torok-Storb and Papayannoupoulo declarations; the specification as filed did not enable the claimed methods at the time the invention was made as they encompass the peripheralization/mobilization and harvesting of hemopoietic stem and progenitor cells, which is the focus of both appellant's arguments and the rejection of record.

With respect to appellant's arguments concerning linking the enablement requirements to the written description requirement, it is maintained that appellant's arguments including the declaratory evidence rely upon the recitation of the claimed methods as they read on peripheralizing/mobilizing hemopoietic stem and progenitor cells. However, neither the recitation of the claimed methods nor a discussion of causing the release of hemopoietic stem and progenitor cells finds written support in the specification as filed for the reasons above. Therefore the specification, in turn, does not provide guidance and direction to the claimed methods for the very methods encompassed, intended and argued by appellant in conjunction with the declaratory evidence.

The application must be enabled at the time the invention was made.

As appellant argues in conjunction with the declaratory evidence, the instant claims encompass and are intended to encompass the peripherilization and harvesting of VLA-4-expressing hemopoietic stem and progenitor cells by administering anti-VCAM antibodies in vivo.

However as pointed out of record and addressed above; appellant's arguments nor the Torok-Storb and Papayannoupoulo declarations (Exhibits D-F) have not pointed out the direction and guidance in the specification as filed as it reads on the claimed blocking of VLA-4 expressing cells to the bone marrow stroma with VCAM-specific antibodies to peripheralize/mobilize or to harvest hemopoietic stem and progenitor cells. The specification as filed does not provide direction and guidance to administer anti-VCAM antibodies for the purpose of mobilizing hemopoietic stem and progenitor cells, as encompassed by the claimed invention and asserted by appellant's arguments and declaratory evidence. Further, it is noted that the instant specification does not provide a working example of blocking hemopoietic stem and progenitor cells from bone marrow stroma either in vitro or in vivo.

It is noted that the observations set forth in the Papayannoupoulo declaration (Exhibit F) rely upon observations on the peripherilization of hemopoietic stem and progenitor cells after the in vivo administration of anti-VCAM antibodies in mice, which did not occur until appellant's priority date and after earlier studies of inhibiting hemopoietic cell/stromal cell interactions in vitro. See the next paragraph based upon Papayannoupoulo (PNAS, 1995; Exhibit 1 of the Brief) for discussion.

Papayannoupoulo (PNAS, 1995; Exhibit 1 of the Brief) discusses the art known limitations at the time the invention was made (see page 9647, column 2, paragraph 1 in particular). In vitro studies have concluded that adhesive interactions between hemopoietic cells and the bone marrow stroma mediated through several cytoadhesion pathways are responsible for anchoring of hemopoietic cells in bone marrow. However, it is noted that the cited references 7-15 all have a publication date of 1991 or later, which is after appellant's priority date of 1990. Further in this paragraph, Papayannoupoulo states that cultured bone marrow stromal cells used may not faithfully reproduce the complex hemopoietic microenvironment in vivo and that the relevance of these in vitro studies to the in vivo bone marrow recognition has not been explored. It is noted that this ability to inhibit hemopoietic cell:stromal cell interactions in vitro relied upon the ability of antibodies to prevent adherence between cells and their microenvironment and did not analyze whether these interactions were reversible or pertuable after adherence has taken place, which is encompassed by the asserted and claimed methods of mobilizing or peripheralizing hemopoietic cells. With respect to in vivo studies, it is noted that page 9651, column 1 paragraph 2 of this reference also refers to reference 23 by Papayannoupoulo et al. (PNAS, 1993) to support the ability of anti-VCAM antibodies to decrease hemopoietic progenitor homing to the bone marrow and to cause their mobilization in normal animals. Again, the objective evidence of record indicates that the ability to mobilize hemopoietic cells with anti-VCAM antibodies was not determined until 1993, which is after appellant's priority date of 1990. Therefore, Papayannoupoulo, as evidenced by (PNAS, 1995; Exhibit 1 of the Brief) supports the lack of enablement of the claimed methods at the time the invention was made, which encompass the peripheralization/mobilization or harvesting of hemopoietic cells for bone marrow transplantation.

As pointed out above, the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies in various methods, but not to the claimed methods nor to methods asserted and encompassed by the claimed methods which encompass methods to peripheralize/mobilize hemopoietic cells in order to harvest hemopoietic stem and progenitor cells for bone marrow transplantation.

In contrast to appellant's assertions and declaratory evidence, the application as filed does not provide sufficient guidance and direction on "how to use" anti-VCAM-1 antibodies to block any VCAM-1-mediated adhesion, regardless of the type of cells involved, which encompasses methods to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells.

Therefore, the specification as filed does not provide any guidance on "how to use" the VCAM-1 specific antibodies in the manner encompassed by the claims or argued by applicant in conjunction with Torok-Storb and Papayannoupoulo or any other manner as encompassed by the claimed methods. The specification is drawn to inhibiting lymphocyte adherence not hemopoietic stem and progenitor cell adherence. The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods.

Appellant's arguments are not found persuasive.

(11) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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